REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1, 5, 7-14, 16-17 and 24 are pending. Applicants elect Group I (claims 1, 5, 7-11 and 24) with traverse. Applicants reserve the right to prosecute the nonelected subject matter in a further patent application.

Notwithstanding the above election, reconsideration of the restriction requirement is requested because examination of all pending claims would not constitute a serious burden. Although the inventions identified by the Examiner are separately patentable, both the need for compact prosecution and the public interest would be served by examination of all claims in a single application. Importantly, all of the claims pending in this application have already been searched in previous Office Actions (four including one that was withdrawn by the previous Examiner). There should be no serious burden to continue examination by giving the previous Examiner's searches the "full faith and credit" required by M.P.E.P. § 704.01:

> When an examiner is assigned to act on an application which has received one or more actions by some other examiner, full faith and credit should be given to the search and action of the previous examiner unless there is a clear error in the previous action or knowledge of other prior art. In general the second examiner should not take an entirely new approach to the application or attempt to reorient the point of view of the previous examiner, or make a new search in the mere hope of finding something.

Therefore, claims 12-14 and 16-17 should not be withdrawn from consideration unless clear error is identified in past examination of this application by the present Examiner and Applicants have the opportunity to reply. If this requirement is maintained despite its traversal, he is respectfully requested to provide evidence of the previous Examiner's clear error.

In the alternative, Applicants disagree with the allegation in the Action that the pending claims lack unity of invention, and therefore belong to different groups of inventions. Although they agree with the Examiner's conclusion that the inventions are separately patentable, Applicants' traversal is based on the pending claims being so linked as to form a single general inventive concept under PCT Rule 13.1. Here, claim 1 is drawn to an assay for determining of a subject's coping capacity for exposure to a

psychological stressor. The result of such assays can be used in a variety of different applications of general interest. In particular, claims 12-14 and 16-17 are drawn to methods using the result of the assay of claim 1. The nonelected claims require that the method according to claim 1 be practiced because claims 12-14 and 16-17 depend from claim 1. Therefore, the pending claims do not lack unity of invention because they refer to the same assay steps. Thus, the limitations (a) to (e) of claim 1 provide the special technical feature shared the pending claims.

Mikawa (Can. J. Anaesth. 40:1162-1170, 1993) was cited in the Office Action as allegedly teaching a technical feature of Applicants' claims. But the relationship between any stress and the induction of superoxide production in neutrophils by a chemical (see page 2 of the Office Action) is **not** the special technical feature comprising claim 1's (a) to (e). Applicants have previously distinguished their invention over Mikawa.

Applicants' invention as claimed is a method for objectively assessing psychological stress. Claim 1 explicitly requires that the method determine coping capacity for exposure to a psychological stressor (where coping capacity is defined as responsiveness of a whole blood sample to induction of superoxide production). The effect of psychological stress is quantified by the claimed method. It still appears that there exist many differences between the claims as properly construed and how they are being construed by the Examiner. In particular, the distinction between control samples and basal readings on test samples and control samples, which is essential for proper understanding of the invention, needs to be correctly recognized. For example, Mikawa takes a second sample after general anesthesia and surgical treatment. This immediately precludes any relevance to determining effect of a psychological stressor. Applicants' claimed invention concerns quantifying the effect of psychological stress. Psychological stress demands that the brain is aware of a stressor; the whole point of general anaesthesia is to make the patient unaware of pain and surroundings plus surgery itself affects the activation of neutrophils. Indeed, this is what Mikawa confirmed in neonates and infants. According to Applicants' invention, differences must be quantified in test (i.e., after exposure to a psychological stressor) compared to control (i.e., substantially free of stress-induced activation or at least derived from a subject to the same condi-

tions minus the stressor) samples, and defining coping capacity as responsiveness of a whole blood cell sample to induction of superoxide production by a chemical inducer which stimulates superoxide production in neutrophils.

A psychological stressor will itself induce superoxide production in neutrophils of a human or non-human animal susceptible to the stressor. The essence of the invention is to determine residual capacity of neutrophils in a whole blood sample for superoxide production in the presence of an added chemical inducer as a measure of stress effect. It is imperative to note that measurements of superoxide production are made on whole bloods samples (not isolated neutrophils) and the method requires comparison of chemically-induced superoxide production above basal (i.e., without inducer) in a test sample and a control sample. Where a test sample is from a subject to the effects of psychological stress, the sample will give lower superoxide production above basal compared with the control. The degree of chemically-induced superoxide production above basal in the test sample will be a measure of coping capacity for exposure to the psychological stressor of concern: e.g., psychological stress in a human arising from taking a written test (see Example 4). This concept for quantifying the effect of a psychological stressor by a **simple whole blood test** relying on determining residual capacity of neutrophils for superoxide production in whole blood samples is not taught or suggested in the cited document.

Mikawa neither teaches nor renders obvious a procedure suitable for objectively assessing any effect of psychological stress. A sample was taken prior to anesthesia, but the next sample was taken was after surgery. This necessarily means that nothing can be gleaned from Mikawa's studies about the effect of psychological stress, which may have occurred prior to surgery. Mikawa's disclosure is only concerned with effects of surgical treatment. Surgery is physical trauma; it is incorrect to equate surgery with psychological stress. Psychological stress demands that the patient's mind is aware of the stressor, while the whole point of general anesthesia is to make the patient unaware of pain. No studies were done using test samples and appropriate controls designed to look at pre-surgical events as a psychological stressor. Mikawa was concerned with looking at how the entire experience of surgery affects neutrophil activity in neonates

and infants against the hypothesis that this could be a contributor to the incidence of post-operative infection. The failure to obtain time points prior to surgery limits Mikawa's conclusions to the effects of physical stress (cf. Example 8 of the specification).

As already attested by an inventor Dr. Rubina Mian, "There is simply nothing in the disclosure of the Mikawa et al. paper which is remotely of interest" to the claimed invention (see Mian Declaration at paragraph 12). Mikawa's mention of PMA, neutrophils, and superoxide production does not make it relevant to the claimed invention. Not only is Mikawa's teachings solely confined to looking at the effect of surgical treatment on neutrophils, it is also important to note that Mikawa chose to use a fixed quantity of isolated neutrophils for stimulation with inducer. Applicants' invention as described in the present specification lies in the discovery that neutrophils should not be isolated prior to being used as a biomarker in whole blood assays for objective assessment of psychological stress. Mikawa discloses that surgery affects leucocyte reactivity. This might be interesting for those concerned with improving recovery from surgery, but the cited document has no relevance to finding an improved method of assessing psychological stress.

Applicants' claims require the use of whole blood samples. The main argument with respect to Mikawa is not, however, centered principally on the type of sample. It is that Mikawa is not relevant prior art. A pre-operative period might give rise to psychological stress in certain individuals, but it is emphasized that Mikawa did not look at this. It is unacceptable to construe the term "psychological stressor" as being reasonably interpreted to include a situation in which surgery under general anesthesia is performed. Looking at any of Mikawa's figures, it can be seen that a first sample was taken before anesthesia to act as a first point for looking at neutrophil changes during the whole peri-operative period. But it cannot be ignored that the second sample was taken during surgery. This immediately excludes any information being revealed about psychological stress in the pre-operative period (or even post-operative period).

Claim 1 sets forth the significant features which distinguish the claimed invention over the art of record. All of the pending claims require an assay drawn to determining the effect of exposure to psychological stress. This cannot be confused with the surgical

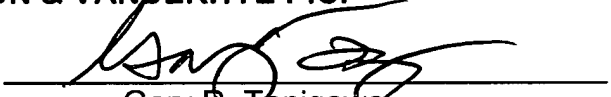
treatment studied in Mikawa. The present claims also require that neutrophils are used as biomarkers for coping capacity (stress effect) without isolation from whole blood samples. It would be improper to construe the claims too broadly to be reasonable.

For the foregoing reasons, Applicants submit that unity of invention is not lacking. Therefore, the pending claims should be examined together in the same application. The counterpart application in Europe was granted last year. The attached patent EP 1558929 B1 demonstrates that the limitations of the present claim 1 were recognized as having inventive step over the prior art.

Applicants earnestly solicit an early and favorable examination on the merits. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

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